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Long-term evaluation of the ocular surface in patients with Behçet's disease

The ocular surface in Behçet's disease

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Abstract

Aim: In this study, we aimed to assess long-term alterations in the corneal epithelium and the ocular surface tests of patients with Behcet disease (BD) and compare the results with those of healthy controls.

Material and Methods: Forty-five patients with BD and 43 healthy subjects were included in this retrospective case-control study. Corneal epithelial thickness (CET) mapping was measured with anterior segment optical coherence tomography (AS-OCT). Noninvasive tear film break-up time (NIBUT) and meibography were measured with corneal topography. Schirmer 1 test, ocular surface disease index (OSDI), tear film break-up time (TBUT) and ocular surface staining score were reviewed. All patients had non-ocular BD. All parameters were re-evaluated annually in the 1st, 2nd and 3rd years of control.

Results: The CET was significantly thicker in the central, inferonasal, inferior and inferotemporal quadrants in the BD group compared with healthy controls (p=0,03, p=0,01, p=0,0001, p=0,001, respectively). The mean TBUT, NIBUT were shorter and the mean OSDI score was higher in the BD group compared to the control group, significantly (p=0,021, p<0,0001, p<0,0001, respectively). Meibography scores showed higher drop-out rates in the inferior eyelid in the BD group (p=0,003). Dry eye tests were improved in Bahçet's patients with dry eye disease after treatment of DED. The difference between the baseline values and values of three consecutive years were statistically significants.

Discussion: Ocular surface changes and DED are more common in BD. Ocular surface and dry eye disease should be carefully evaluated and treated in BD patients to avoid untreatable complications of the cornea.

Keywords

Behcet's Disease, Corneal Epithelium, Meibography, Tear Breakup Time, Dry Eye

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Introduction

Behcet disease (BD) is a relapsing multisystemic vasculitic disorder characterized by immune-mediated occlusive vascular involvement, recurrent and episodic uveitis, oral ulcers, genital ulcerations, and skin lesions [1]. Typically, the onset of the disease in the third decade of life [2]. Although the severity may be asymmetrical, ocular BD is bilateral in the majority of the patients [1]. It has a worldwide distribution but is most common in Japan, the Middle East, and Mediterranean countries. The prevalence rate of the disease in Turkey is 20–602/100,000 cases [3].

BD is characterized by occlusive-vasculitis ischemic changes, and hemodynamic changes in conjunctival vessels similar to well-known vessel changes in the retina [4-6]. Therefore, besides uveitis, BD can lead to conjunctivitis, conjunctival ulcer, episcleritis, and scleritis [7,8]. The disease is associated with vasospasm. Goblet cell density depends on vascularization and factors in conjunctival blood circulation. These cells are very sensitive to abnormal situations. Any inflammation of the ocular surface can lead to squamous metaplasia in epithelial cells and loss of glycocalyx and goblet cells [9,10]. A limited number of studies about changes in the ocular surface and dry eye disease have been identified in the literature. These studies support the existence of an ocular surface disease in patients with BD.

The aim of this study is to describe the long-term alterations in the corneal epithelium and the ocular surface tests of patients with BD and compare the results with those of healthy controls.

Material and Methods

This is a retrospective case-control study. We retrospectively evaluated the records of 45 patients with non-ocular BD at Diskapı Yildirim Beyazit Training and Research Hospital, Ankara, Turkey between January 2022 and January 2023. Ethical approval was obtained from Diskapı Yildirim Beyazit Training and Research Hospital Ethics Committee on 30/06/2015 with issue no: 24/07 and the study was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to the ophthalmologic examination.

All patients were Turkish Caucasians with non-ocular BD. In this study, the diagnosis of BD was reached according to the criteria of the International Study Group for BD. Cases who reported nonsteroidal anti-inflammatory drug (locally/systemically), and steroid (locally/systemically) use within the past 6 months, previous punctal plug, contact lens wear, use of other topical treatments, active ocular infection, blepharitis, recurrent herpes keratitis within the previous 6 months, ocular surgery or trauma within the previous 6 months, punctate epithelial erosions of the cornea, other ocular surface diseases, and non-keratoconjunctivitis sicca inflammation, including atopic keratoconjunctivitis were excluded from this study. None of the patients had a history of Stevens-Johnson syndrome, chemical, thermal, or radiation injury, or any ocular surgery that would create an ocular surface problem. Patients with a history of systemic disease other than BD were excluded. None of the patients had a history of smoking or alcohol consumption. None of the patients in the BD group had a history of using diuretics, antihistamines, vitamins, antianxiety medications, antidepressants, and any medications with anticholinergic properties. Age and sex-matched control group was recruited with the same exclusion criteria, had no ocular problems, no history of ocular surgery, and no major systemic disease affecting the ocular tissues.

Detailed medical records of patients including corneal epithelial thickness (CET) mapping derived from anterior segment optical coherence tomography (AS-OCT) (RTVue-XR, Optovue Inc., USA) and dry eye disease (DED) tests: noninvasive tear film break-up time (NIBUT), and meibography, which were measured with corneal topography (Sirius; Costruzione Strumenti Oftalmici (CSO), Florence, Italy), Schirmer 1 test, ocular surface disease index (OSDI), tear film break-up time (TBUT) and ocular surface staining score (according to the DEWS II 2017 report) [11] were reviewed.

CET measurements were carried out by the same experienced technician with the AS-OCT. The image analysis system (Software version 5.5) of the non-contact anterior segment module automatically interprets the mean CET. Scans were performed in 17 sectors along a diameter of 6 mm with the pupil centered. The average CET of each sector can also be calculated (Figure 1). Three consecutive measurements were performed and the measurement with the best signal was employed for the study.

OSDI is a questionnaire consisting of twelve questions and aims to question the patient's complaints of dry eye. In addition to the symptoms themselves, the effects of these complaints on daily activities and the environmental triggering factors are investigated. The severity of the disease is graded by scoring the duration and severity of the complaints. Results are evaluated on a scale from 0 to 100, with increasing scores indicating increasing severity of dry eye [12,13].

Tear film breakup time (TBUT)

Fluorescein-soaked paper strips (Bio Glo Sterile Strips, Rose Stone Enterprises, CA, USA) were soaked in saline and then placed in contact with the lower fornix to determine the TBUT. After waiting for fluorescein diffusion, the cobalt blue filter on the slit lamp was used to evaluate the tear film. The time from the patient's last blink to the appearance of the first dry spot was measured three times and the mean value was calculated [14].

Ocular surface fluorescein staining After the TBUT measurement, the ocular surface was evaluated using the cobalt blue filter of the slit lamp following fluorescein administration. The Oxford Scheme was used to classify fluorescein ocular surface staining into six stages [15,16]. Dry eye disease diagnosis was made according to the DEWS II dry eye report [11]. Parameters of the BD group were re-evaluated annually in the 1st, 2nd and 3rd years of control.

BD patients diagnosed with dry eye disease were treated with polyvinyl Alcohol-Povidone (5,6 mg PA-2,4 P) and carbomer gel for those without corneal staining and the above treatment plus 0,05% cyclosporine for those with corneal staining.

Statistics

Parameters between BD and control groups were compared using independent- samples t-test, Mann-Whitney U test, Fischer's Exact test, and Chi-squared test where appropriate. The Spearman correlation test was applied to understand the relation between the CET quadrants, which were found to be

different between the BD and control groups, and the DED parameters. P<0.05 was considered statistically different. SPSS version 21.00 was used for statistical analysis.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

A total of 88 cases (45 BD patients, 43 controls) were enrolled in this study. There was no difference between the groups in terms of age and gender. The number of females was predominant in both groups (28 in BD, 33 in the control group, p=0,17). The mean age was 45,06±9,6 in the BD group and 41,81±6,2 in the control group (p=0,06). The mean duration of BD diagnosis was 55,20±36,0 months. The mean follow-up duration was 47,6± 6,4 months. The CET was found thicker in the central, inferonasal, inferior and inferotemporal quadrants in the BD group and this difference was statistically significant (Table 1). CET: Corneal epithelium thickness, BD: Behcet disease, *p <0.05 paired samples t-test.

According to the ocular surface test results, the mean TBUT (BD: 9,2±3,5, control: 10,8±3,0, p=0,021) and NIBUT (BD: 9,85±5,4, control: 14,6±3,7, p<0,0001) was found shorter and mean OSDI score (BD: 25,5±16,6, control: 8,4±15,0) was found higher in the BD group compared to the control group, and these difference was statistically significant (p=0,021, p<0,0001, p=0,0001 respectively). Meibography scores showed significant drop-out rates in the inferior eyelid in the BD group (p=0,003).

Table 1. Comparison of CET of the sectors between the Behcet disease group and control group.

CET of sectors	BD group	Control group	P value
Central	53,56±3,34	52,02±3,15	0,03*
Superior	50,24±4,21	50,44±4,13	0,83
Superonasal	50,26±3,26	50,37±3,7	0,9
Nasal	51,53±4,9	51,05±2,94	0,58
Inferonasal	53,73±3,25	51,72±3,91	0,01*
Inferior	54,02±2,9	50,88±3,52	0,0001*
Inferotemporal	53,71±3,4	51,37±2,89	0,001*
Temporal	51,36±4,60	50,16±3,09	0,17
Superotemporal	50,67±3,93	49,95±3,73	0,34

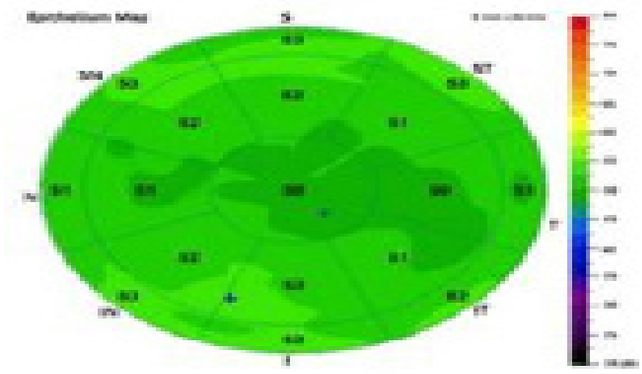

Figure 1. Corneal epithelial thickness measurements with anterior segment optical coherence tomography.

Table 2. Comparison of the CET of the sectors in the BD group at the 1st visit and three consecutive annual controls (baseline to 3 years)

CET	Baseline	1 year	2 years	3 years	P Value
Central	53,56±3,34	53,12±2,58	53,16±2,49	53,13±2,43	0,11
Superior	50,24±4,21	50,24±3,9	50,33±3,89	50,4±4,03	0,38
Superonasal	50,26±3,26	50,27±2,99	50,31±2,99	50,28±2,93	0,87
Nasal	51,53±4,9	51,58±4,56	51,44±4,74	51,51±4,75	0,25
Inferonasal	53,73±3,25	53,38±2,65	53,49±2,70	53,44±2,69	0,039
Inferior	54,02±2,9	53,84±2,58	53,83±2,57	53,87±2,62	0,27
Inferotemporal	53,71±3,4	53,62±3,23	53,51±3,06	53,67±3,53	0,67
Temporal	51,36±4,60	51,11±4,24	51,24±4,39	51,27±4,2	0,09
Superotemporal	50,67±3,93	50,71±3,79	50,67 ±3,69	50,69±3,84	0,63

CET: Corneal epithelium thickness, BD: Behcet disease, *ANOVA test

Table 3. Comparison of the DED tests and meibography scores in the BD group at the 1st visit and three annual consecutive controls.

	Baseline	1 year	2 years	3 years	P Value
Schirmer 1, mm	21,4±11,5	23,89±8,9	24,96±7,12	25,13±7,02	0,0001*
TBUT, sec	9,2±3,5	10,84±2,08	10,84±1,8	11,11±1,68	0,0001*
NIAvgBUT	9,85±5,4	11,21±4,20	12,08±3,6	12,56±3,3	0,0001*
Fluorescein staining, grade	2,13±0,73	0,87±0,35	0.84±0.32	0.79±0.40	0,01*
OSDI score, points	25,5±15,0	21,43±11,25	19,73±9,64	18,52±9,5	0,0001*
Superior Meibography, %	24,12±14,5	23,87±13,86	23,89±14,08	23,9±14,07	0,063
Inferior Meibography, %	27,73±16,79	27,70±16,7	27,69±16,7	27,74±16,8	0,072

dry eye disease, BD: Behcet disease, *ANOVA test

All parameters were re-evaluated annually in the 1st, 2nd and 3rd years of control in the BD group. As the baseline values were compared with the 1st year control, the difference in the CET was found significantly greater only in inferonasal quadrants (p=0,039) (Table 2). There was a significant improvement in dry eye tests in Bahçet's patients with dry eye disease after treatment of DED. The difference between the baseline values and values of three consecutive years were statistically significants. (p<0,01) (Table 3). Meibography score values did not show a statistically significant difference.

Discussion

BD is a vasculitic disorder in which the eye is one of the most commonly involved organs. Systemic inflammatory diseases are generally represented with DED [17]. Gunduz et al. found that Schirmer 1 and TBUT were worse in BD [18]. They also reported that no differences were found in the conjunctival cell morphology or in the impression cytology results between BD with or without ocular involvement.

No studies were found in the literature in regard to corneal epithelium in patients with BD. There are conflicting results on the CET and DED relationship in the literature. To the best of our knowledge, this is the first study to evaluate the long-term changes in the corneal epithelium and its relation with DED in cases with BD.

According to our results, we revealed changes in the corneal epithelium in the BD group, where the corneal epithelium was found to be thicker in the central, inferonasal, inferior and inferotemporal sectors. Patients in the BD group were more prone to have DED as the ocular surface test results were found worse than in the control group.

In an AS-OCT study, the inferior CET was found to be thicker in patients with DED [19]. The mean NIBUT of the DED group was 7.2±1.3. The results of the study above were explained by the possible hypertrophy/hyperplasia of the epithelial cells and an increase in the number of the cellular layers due to the insults inflicted by the tear film deficiency. Kanellopoulos and Asimellis conducted a study that evaluated CET with AS-OCT in patients with DED [20]. They reported that the central and average overall CET was thicker compared to the control group. Their explanation was the same as that of the authors of the formerly mentioned study for CE thickening. The results of these studies showed corneal epithelial thickening in parts of the cornea cases with DED. In our study, cases with BD had thicker corneal epithelium in the inferior and the superonasal quadrants. In our study, it is quite difficult to understand whether the corneal epithelium change is due BD or due to ocular surface changes due to BD.

On the other hand, Ciu et al. showed that only superior CET was thinner in DED [21]. They suggested that alterations in the tear film in DED made the superior CE more vulnerable to mechanical friction caused by the upper eyelid. Liang et al. reported that mean limbal CET was thinner in DED and inferior limbal CET was correlated with OSDI, Schirmer I test, BUT, Oxford score [22]. Besides, in a study of in vivo confocal laser scanning microscopy, peripheral corneal epithelial thickness was found to be smaller in dry eye patients and DED parameters demonstrated a significant correlation with CET in the lower periphery [23].

Our study results revealed thicker CET, lower mean TBUT and NIBUT lower and higher mean OSDI score in BD group at their first visit. The corneal staining scores were also higher in the BD group. As cases with DED in the BD group were treated for DED according to the treatment algorithms of the TFOS DEWS II report, a significant improvement was noted in the corneal epithelium and ocular surface test results in the annual evaluations of these patients.

We think that thickening in the CET seen in the inferior quadrants might be due to the fact that pro-inflammatory cells accumulated in the inferior sac are in contact with the inferior cornea in the association of DED and BD more than the superior quadrants. One of the significant outcomes of the present study was the increased thickness of CE in the inferior quadrants, probably caused by epithelial hyperplasia/ hypertrophy and swollen cells due to severe DED in BD.

Limitations

This study is a long-term follow-up of the ocular surface in BD, evaluating dry eye tests and the corneal epithelium, which makes our work valuable. Nevertheless, this study has some limitations. First, the duration of the DED in BD was not known since the DED diagnosis was made for the first time at the 1st visit. In addition, no evaluation was conducted on analyzing inflammatory reaction and osmolarity. Thus, we believe that further studies should be conducted with more comprehensive analysis of inflammatory cytokines and osmolarity to evaluate the definite effect of BD on corneal epithelium and DED. On the other hand, with the strict inclusion and exclusion criteria and patients who used all detailed tests, we think the number of patients included in this study was reasonably sufficient.

Conclusion

In conclusion, we believe that as an inflammatory systemic disease, patients with BD are more likely to have ocular surface changes and DED. Therefore, the ocular surface and dry eye disease should be carefully evaluated and treated in BD patients to avoid untreatable complications.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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